REMARKS

Status of the Claims

Claims 1-3, 8-13, 39-40, and 42 are cancelled without prejudice.

Claims 21-23 and 30-38 stand withdrawn pursuant to the restriction requirement.

Applicant expressly preserves the right to pursue any of the foregoing claims in a subsequent continuation or divisional application.

The allowance of claims 5-7 is noted with appreciation.

The amendments to the remaining claims 4, 14-20, 24-29, 41 and 43 are discussed in detail below.

Specification

The specification has been amended to recite the fact that the applicant is claiming the benefit under 35 USC 371 of International Application No. PCT/GB04/002871, having an international filing date of 01 July 2004 and claiming a priority date of 01 July 2003.

As the information concerning the benefit claim was previously submitted within the time period set forth in 37 CFR 1.78(a), and was recognized by the Office as shown by its inclusion on the filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required, as per the first full paragraph on page 4 of the Office Action.

Claim objections

Claim 43 has been amended to change "claims" to "claim" for grammatical accuracy. The same correction was made in claim 41. No change to the scope of the claim is intended by this amendment.

Claim rejections – 35 USC § 112 second paragraph

Claims 15 and 16 have been rejected under 35 USC 112 second paragraph. Claim 15 has been amended to recite that an effector molecule is attached to an engineered cysteine in the light chain constant region and/or to an engineered cysteine

in the heavy chain constant region, and claim 16 has been cancelled. It is respectfully submitted that these amendments render claim 15 sufficiently definite to overcome this ground of rejection.

Claim rejections – 35 USC § 112 first paragraph

The extensive discussion of the rejection of claims 15-16, 20, and 24-29 as failing to comply with the written description requirement was based on the prior version of these claims. It is respectfully submitted that the present amendments to these claims are sufficient to overcome the written description rejection. In particular, the Examiner's attention is directed to the description of attachment of effector molecules at page 12, and to Example 1, wherein reductants are discussed.

Claim rejections – 35 USC § 102

Claims 1-4, 8-15, 17-18, 39-40 and 42-44 were rejected under 35 USC 102(b) as being anticipated by Carter as evidenced by Bodmer et al. Claims 1-3, 8-13, 39, 40, 42, and 44 have been cancelled without prejudice. Thus the only claims still subject to this rejection are claims 4, 14, 15, 17, 18, and 43.

Claim 4 has been amended to recite, *inter alia*, that the hinge region of the claimed antibody fragment is modified to comprise SEQ ID NO: 1 or SEQ ID NO: 2. It is respectfully submitted that an antibody fragment of this structure is not found in either the Carter or Bodmer references. Claim 14 has been amended to recite, *inter alia*, that each effector molecule is PEG or a derivative thereof. It is believed that this feature also is not disclosed in either the Carter or Bodmer references. Therefore claim 14, and claims 15, 17, and 18 which depend from claim 14, are not anticipated. Claim 43 is multiply dependent on claim 14 or claim 24, which also has been amended to recite PEG (or PEG derivative) effector molecules. It is therefore respectfully submitted that the rejection of these claims as anticipated by Carter as evidenced by Bodmer has been overcome.

Claims 1-2, 4, 8-15 and 39-44 were rejected as anticipated by Hsei et al. Claims 1-2, 8-13, 39, 40, 42, and 44 have been cancelled without prejudice. Thus the remaining claims subject to this ground of rejection are claims 4, 14, 15, 41, and 43.

As noted above, claim 4 has been amended to recite, *inter alia*, that the hinge region of the claimed antibody fragment is modified to comprise SEQ ID NO: 1 or SEQ ID NO: 2, which feature is not disclosed in Hsei. Claims 14 and 24 each recite that the antibody fragment is a Fab or Fab' fragment, and that there are at least two effector molecules. Referring to page 23 of the Hsei reference, Hsei teaches at lines 4-5 that two polymer molecules can be attached when the fragment is $F(ab')_2$, and at lines 9-11 that only one polymer molecule is attached when the fragment is Fab, Fab', or Fab'-SH. Note also in Hsei page 24, line 24– page 25, line 32, wherein the fragment is $F(ab')_2$ and there are **two** polymers attached; and page 25, line 33 – page 28, line 4 wherein the fragment is selected from Fab, Fab', or Fab'-SH and there is **only one** polymer attached. Claims 14 and 24 of the present application recite that the fragment is Fab or Fab', yet has **two** polymer molecules attached. This structure is not disclosed in Hsei, therefore these claims are not anticipated. Claim 15, which depends from claim 14, and claims 41 and 43 which are each multiply dependent on claims 14 and 24, also are not anticipated.

Claim rejections – 35 USC § 103

Claims 1-3 were rejected under 35 USC 103 as obvious over Hsei et al. in view of Humphreys. As claims 1-3 are now cancelled without prejudice, this ground of rejection is now rendered moot.

Claims 24-29 were rejected under 35 USC 103 as obvious over Singh et al. in view of Hsei et al. and Humphreys. Claim 24 is now amended to recite that the antibody fragments have at least two or more effector molecules attached thereto, the effector molecules being attached to each of the interchain cysteines, which effector molecules are either PEG or a derivative thereof. At the time of the priority date of the present invention, one skilled in the art would not have attempted to attach PEG (or a derivative) to the interchain cysteines of a Fab or Fab' fragment because of the risk that the PEG would draw water away from the antibody fragment, creating a destabilizing effect on the fragment that would force the heavy and light chains apart. The inventors herein discovered that, surprisingly, and contrary to prior perceptions in the art, an antibody fragment can be provided with PEG effector molecules attached to the interchain cysteines, and the heavy and light chains remain associated with each other, such that the PEGylated antibody Fab' fragment has equivalent antigen binding

and *in vivo* activity compared to PEGylated Fab' fragments in which the interchain disulphide bond is present.

Singh et al. describes only the attachment of small molecules such as biotin to a whole antibody, not larger molecules such as PEG to an antibody fragment. Hsei teaches fragments in which one of the interchain cysteines has been substituted with serine, and no more than one polymer is attached to the fragment, the attachment being at the remaining interchain cysteine. Claim 24, however, requires that an effector be attached to both interchain cysteines. Humphreys WO99/15549 is concerned with the production of dimeric $F(ab')_2$ fragments containing a specific hinge sequence having four cysteines. Humphreys discloses fragments in which **both** interchain cysteines have been replaced with serines. Humphreys makes no mention of fragments in which both the interchain cysteines were retained and have effector molecules attached. Thus combining Singh, Hsei, and Humphreys would not result in the product of claim 24, namely a fragment having PEG attached to **both** its interchain cysteines , and there is no teaching or suggestion in the combined art to create such a structure.

As all points of rejection have been overcome, a Notice of Allowance is respectfully requested.

Respectfully submitted,

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